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SCRUB TYPHUS

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In conducting the research described in this report the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources Commission on Life Sciences-National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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SCRUB TYPHUS

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Human Disease: Scrub typhus. Synonyms: tsutsugamushi disease, mite-borne typhus, chigger-borne rickettsiosis, Japanese river or flood fever, tropical typhus, rural typhus, and akamushi disease

Animal Model: Scrub typhus in cynomolgus and silvered leaf monkeys

Biological Features: Scrub typhus is caused by Rickettsia tsutsugamushi, an obligately intracellular bacterium, whose vector and principle reservoir is the larval (chigger) stage of the trombiculid mite. The disease is found in an area roughly bounded by Korea, northern Australia, and Pakistan. Manifestations of infection vary greatly, from inapparent disease to death. The mortality rate is generally very low since the advent of chloramphenicol and tetracycline, although some geographic areas in Japan have reported rates of 30% or

higher. Mortality rate appears to be dependent on the strain of R. tsutsugamushi causing the infection.

The disease has been studied in a wide variety of animal models. These include monkeys, mice, rabbits, rats, guinea pigs, gerbils, and dogs. Hamsters, chickens, goats, horses, cats, calves, and pigeons have also been shown to be susceptible to infection with the agent. Definitive evidence for infection with R. tsutsugamushi requires a positive antibody response with a demonstrable rise in titer between the acute and convalescent specimens, and isolation of the agent by mouse inoculation of blood from the animal suspected of being infected.

Pathologic manifestations of scrub typhus at autopsy are not striking. The spleen and lymph nodes are generally enlarged. Hemorrhagic pneumonia with secondary bronchopneumonia is often evident. Rash, which is common during the course of the disease, is rarely seen at autopsy; however, an eschar is often noted at the site of the chigger bite. Microscopically, there is a disseminated, focal, vasculitis and perivasculitis of the small vessels, consisting of monocytes, lymphocytes, and plasma cells. An interstitial pneumonitis is present in almost all scrub typhus fatalities. Vascular changes are generally seen in the heart, lungs, brain, and kidneys. As a result, an acute, nonsuppurative myocarditis of



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varying intensity is characteristic. Brain lesions consist of a few vascular and perivascular reactions, as are seen throughout the body. Similar changes can be seen in the spleen and lymph nodes, with mononuclear cell infiltration in the pulp and sinuses and follicular necrosis. The kidneys characteristically show focal interstitial lesions. These can be associated with adjacent nephron damage¹. The cause of death is generally equally attributed to circulatory failure, secondary pneumonia, or encephalitis².

Work on a monkey model for the disease was begun in 1918 in Japan and reached its peak in the early 1970s. While other species were studied, the most extensively used were the cynomolgus (Macaca fascicularis) and silvered leaf (Presbytis cristatus) monkeys. It was shown that monkeys develop fever, eschar, anorexia, splenomegaly, hepatomegaly, and lymphadenopathy; however, just as in man, these were not universally observed. Rickettsemia and seroconversion were also detectable. Mouse-lethal strains of R. tsutsugamushi generally produced fever in monkeys, concomitant with a decrease in hematocrit, total white cell count, and thrombocytes³.

The selection of a species for use as an animal model for human scrub typhus has not been clear cut. Approximately 45% of wild-caught cynomolgus have antibody to R. tsutsugamushi⁴; however, wild-caught silvered leaf

monkeys rarely have antibody^{4,5}. This has been attributed to the strictly arboreal nature of the silvered leaf monkeys, as opposed to the semi-arboreal cynomolgus, allowing the latter to come into contact with the vector chiggers. Silvered leaf monkeys, on the other hand, are difficult to maintain in captivity without a 40-50% mortality rate³.

Based on the studies completed thus far, the cynomolgus monkey is probably the monkey model of choice for human scrub typhus, due to its clinical response, ease of maintenance, and hardiness compared to those of the silvered leaf monkey. Since it has been demonstrated that cynomolgus breeding colonies are feasible⁶, animals free of R. tsutsugamushi-specific antibody can be made available for scrub typhus research. Laboratory-reared monkeys have been found to exhibit the same response as wild-caught cynomolgus monkeys (personal communication with A. Shirai). Irrespective of the model used, researchers must be aware that a direct correlation of clinical signs and virulence produced by R. tsutsugamushi strains in man and monkeys has not been shown.

Comparisons with Human Disease: The incubation period in man is usually 10-12 days. The disease is characterized by fever, headache, lymphadenopathy, splenomegaly,

malaise, eschar, and a number of other nonspecific signs and symptoms. A generalized rash can occur, starting on the chest, face, and abdomen and spreading outward to the extremities. The rash is usually not seen until 5-6 days after onset of the infection and may last 3-10 days⁷.

Rickettsemia, beginning several days before disease onset and continuing as late as 2-3 days after initiation of antibiotic therapy, can be demonstrated by inoculation of susceptible mice with blood from a suspect patient. Convalescence is generally uneventful.

A study employing intradermal inoculation with either the Karp, Gilliam, or Kato strains of R. tsutsugamushi demonstrated that both cynomolgus and silvered leaf monkeys develop rickettsemia, fever, and regional lymphadenopathy. Those infected with the Gilliam strain developed eschars. In addition, the monkeys also developed antibody titers similar to those reported for man, although the titers in cynomolgus monkeys were greater³. Note that not all of the monkeys developed each of the signs. This variability is similar to what is seen in man.

As in man, R. tsutsugamushi-specific antibody titers decline to barely detectable levels by 1 year post-infection. Immunity to reinfection also declines, in parallel with the decline in antibody levels^{8,9}. A more recent study examined the cell-mediated immune response

in cynomolgus monkeys¹⁰. It was shown that antigen-sensitive lymphocytes can be detected soon after infection, peak at about 2 weeks, and rapidly decline to very low levels after 2 months.

Usefulness of the Animal Model: Cynomolgus and silvered leaf monkeys are most useful for vaccine and pathology studies, as the disease best mimics what is seen in man. The mouse, however, is the animal of choice for the isolation of the agent and for most other experimental studies. Due to the expense in procuring and maintaining monkeys for disease studies, economics may also play a part in the selection of the model to be used. Very little has been done on the pathology of scrub typhus in the monkey.

Availability: Wild-caught cynomolgus and pigtailed (Macaca nemistrina) monkeys often have pre-existing R. tsutsugamushi infections, as demonstrated by positive indirect fluorescent antibody titers². Because titers decline rapidly, the absence of a titer does not necessarily mean that the animal had not been previously infected with R. tsutsugamushi. For this reason, we highly recommend that colony-reared M. fascicularis be used for scrub typhus research studies.

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